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## METHOD FOR FORMING AN AQUEOUS FLOCCULATED SUSPENSION

### BACKGROUND OF THE INVENTION

#### 1. Field of the Invention

The present invention relates to aqueous suspensions of active substances, and in particular, to aqueous flocculated suspensions containing one or more insoluble actives which are suitable for oral delivery. The invention also relates to the use of certain surfactants to enhance flocculation in aqueous pharmaceutical suspensions.

#### 2. Background

There have been many attempts to formulate aqueous suspensions of water-insoluble pharmaceutical active ingredients. Flocculated suspensions in particular are desirable in numerous applications. They are well suited for oral delivery of the active, and are often preferred for patients for whom swallowing pills or other dosage forms is difficult. A flocculated suspension contains the active pharmaceutical dispersed throughout the liquid medium. Minute particles of the active agent associate themselves with one or more excipients to form an agglomerated mass which is referred to as a "flocule" or "floc". Other excipients in turn act to suspend the snowflake-like flocs in the water. The goal is to achieve a dispersion in which the active pharmaceutical component can be uniformly suspended and dispersed upon light to moderate shaking. In this way, the patient can be assured of receiving not only the appropriate dosage of the active, but substantially the same dosage upon each administration.

Many surfactants available in the art act as wetting agents for water-insoluble actives. These wetting agents greatly facilitate the formation of aqueous suspensions by reducing the surface tension between the active and the aqueous phase. Other compounds function as suspending agents which maintain the wetted active in uniform dispersion throughout the liquid media. The problem which arises is finding the right combination of compounds which are best suited for the particular active. Another problem is finding the particular concentration range which will enhance flocculation and ensure adequate flocule size. In addition to achieving good dispersion and uniformity, another goal is ensuring the optimal bioavailability of the active. The flocules should permit the active to be absorbed by the body at a rate and in an amount which will facilitate its efficacy. Moreover, the active should be stable in the aqueous suspension over its entire shelf-life.

Atzinger et al., U.S. Pat. No. 5,338,732, is directed to a flocculated suspension containing the active substance megestrol acetate, together with polyethylene glycol and polysorbate, in particular polysorbate 80. The polysorbate component is present in an amount of 0.005% to 0.015%. At polysorbate 80 concentrations as low as 0.025% the patentees note significant deflocculation and caking of the formulation. In addition, Table 4 in the reference shows a significant decrease in physical stability at a concentration of 0.02% polysorbate 80.

Thus, there exists a need in the art to find a suitable combination of compounds which together with one or more pharmaceutical actives can form a stable flocculated liquid suspension. There also exists a need for an improved flocculated suspension containing one or more actives together with a synergistic amount of one or more excipients. There is a further need in the art to avoid the aforementioned issues associated with the use of polyethylene glycol together with polysorbate in forming a megestrol acetate formulation.

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## SUMMARY OF INVENTION

The invention according to one embodiment is a composition containing at least one insoluble active substance together with at least one wetting agent. The concentration of the wetting agent is sufficient to form a stable, flocculated suspension of the active substance.

Also provided as part of the invention is a method for forming a composition which involves combining at least one active substance and at least one wetting agent, wherein the wetting agent is present in an amount sufficient to form a stable, flocculated suspension of the active substance.

Further provided is a method for forming an aqueous flocculated suspension containing an insoluble active substance together with a wetting agent in which the wetting agent is added in an amount below which the flocule size in the suspension starts to increase.

The invention also provides an oral pharmaceutical composition having about 0.5 to about 10% of megestrol acetate; about 0.01 to about 0.04% of docusate sodium; and about 10 to about 30% of at least one suspending agent.

There is also provided as part of the invention an oral composition having about 1 to about 8% of megestrol acetate, about 15 to about 25% of polyethylene glycol; about 0.01 to about 0.04% of docusate sodium, and about 0.1 to about 0.3% of xanthan gum.

As part of the invention, there is also a method of forming an oral pharmaceutical composition in which a first portion of polyethylene glycol is combined with xanthan gum and water in a first vessel. A second portion of polyethylene glycol, docusate sodium and megestrol acetate is combined in a second vessel. The contents of the first vessel are then combined with the contents of the second vessel.

In another method as part of the invention, an oral pharmaceutical composition is formed by combining a first portion of polyethylene glycol, a first portion of water, docusate sodium and megestrol acetate in a first vessel. Xanthan gum, a second portion of water and a second portion of polyethylene glycol are combined in a second vessel. The contents of the first vessel are then combined with the contents of the second vessel.

Additional advantages and features of the present invention will become more readily apparent from the following detailed description which illustrates various embodiments of the invention.

### DETAILED DESCRIPTION

The pharmaceutical composition of the invention is described as a flocculated aqueous suspension. A suspension is one in which solid particles of one or more active substances are suspended within a liquid medium. The liquid medium may contain various excipients, especially one or more wetting/dispersing agents and suspending agents. These excipients maintain the active in combinations or aggregations of suspended particles known as "flocules" or "flocs" within the suspension.

The composition of the invention is also described as being "stable". A stable suspension is one which can be redispersed or resuspended with light to moderate shaking throughout its shelf-life, thereby resisting caking or sedimentation. In addition, a stable suspension is one which resists changes in flocule particle size and distribution, the suspended active agent is not substantially degraded, nor is its bioavailability substantially affected over the course of its shelf life. The composition of the invention according to the embodiments hereinafter described should be stable, i.e.,